



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.: 10/609,298 Confirmation No.: 9201  
Applicant: Sommadossi *et al.*  
Filed: June 27, 2003  
TC/A.AU.: 1623  
Examiner: Unassigned  
  
Docket No.: 06171.105059 IDX 1017  
Customer No.: 20786  
Title: 2' and 3'-Nucleoside Prodrugs for Treating Flaviviridae Infections

Commissioner for Patents  
P. O. Box 1450  
Alexandria, VA 22313-1450

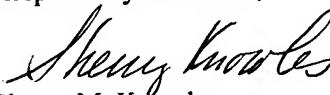
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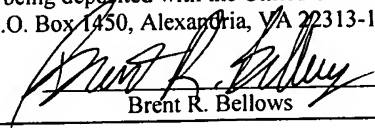
Respectfully submitted,

  
Sherry M. Knowles  
Reg. No. 33,052

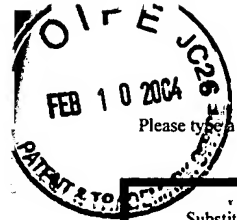
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Sheet 1 of 7

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### U.S. PATENT DOCUMENTS

Examiner Initials *	Cite No. <sup>1</sup>	U.S. Patent Document		Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages/Relevant Figures Appear	T <sup>6</sup>
		Number	Kind Code (if known)				
	AA	3,798,209		Wilkowski, <i>et al.</i>	03-19-1974		
	AB	RE29,835		Witkowski <i>et al.</i>	11-14-1978		
	AC	4,522,811		Eppstein <i>et al.</i>	06-11-1985		
	AD	4,957,924		Beauchamp	09-18-1990		
	AE	5,149,794		Yatvin <i>et al.</i>	09-22-1992		
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	AG	5,194,654		Hostetler <i>et al.</i>	03-16-1993		
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	AQ	DE	3,512,781	A1	Soc. Nat. Elf Aquitaine	10-17-1985		
	AR	EP	0,180,276	B1	Stamicarbon B.V.	12-19-1988		
	AS	EP	0,350,287	B1	Chimerix	09-27-2000		
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	AU	WO	89/02733	A1	Regents of the Univ. of California	04-06-1989		
	AV	WO	90/00555	A1	Vical Inc.	01-25-1990		
	AW	WO	91/16920	A1	Vical Inc.	11-14-1991		

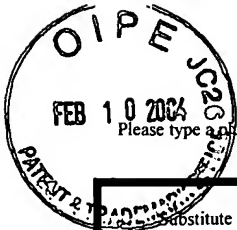
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	BA	WO	91/18914	A1	Vical Inc.	12-12-1991		
	BB	WO	91/19721	A1	Glazier	12-26-1991		
	BC	WO	93/00910	A1	Vical Inc.	01-21-1993		
	BD	WO	94/26273	A1	Hostetler	11-24-1994		
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	BF	WO	99/15194	A1	Schering Corporation	04-01-1999		
	BG	WO	99/43691	A1	Emory; U. Georgia Res. Found.	09-02-1999		
	BH	WO	99/45016	A2	Metabasis Therapeutics Inc.	09-10-1999		
	BI	WO	99/59621	A1	Schering Corporation	11-25-1999		
	BJ	WO	99/64016	A1	Hoffman-La Roche AG	12-16-1999		
	BK	WO	00/24355	A1	Smith & Nephew Kinetic	05-04-2000		
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	BU	WO	01/92282	A2&3	Novirio (Idenix); Univ. ... Cagliari	06-12-2001		
	BV	WO	01/96353	A2&3	Novirio Pharm. (Idenix); C.N.R.S.	21-20-2001		
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	BX	WO	02/057425	A2	Merck; Isis Pharmaceuticals	07-25-2002		
	BY	WO	02/18404	A2&3	Hoffman-La Roche AG	03-07-2002		
	BZ	WO	02/32414	A2&3	Schering Corporation	04-25-2002		
	BAA	WO	02/32920	A2	Pharmasset	04-25-2002		
	BAB	WO	02/48165	A2&3	Pharmasset	06-20-2002		
	BAC	WO	03/024461	A1	Schering Corporation	03-27-2003		

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		Office <sup>3</sup>	Number	Kind Code <sup>2</sup> (if known)				
	CA	WO	04/003138	A2	Merck & Co., Isis Pharmaceutical	01-08-2004		
	CB	WO	04/003138	A2	Merck & Co., Isis Pharmaceutical	01-22-2004		
	CC	WO	04/009020	A2	Merck & Co., Isis Pharmaceutical	01-29-2004		

**OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS**

Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	CD	BAGINSKI, S. G. <i>et al.</i> , "Mechanism of action of a pestivirus antiviral compound," <i>PNAS USA</i> , 97(14): 7981-7986 (2000).	✓
	CE	BATTAGLIA, A.M. <i>et al.</i> , "Combination Therapy with Interferon and Ribavirin in the Treatment of Chronic Hepatitis C Infection", <i>Ann. Pharmacother</i> , 34:487-494 (2000).	✓
	CF	BERENGUER, M. <i>et al.</i> , "Hepatitis C virus in the transplant setting", <i>Antivir. Ther.</i> , 3 (Suppl 3):125-136 (1998).	✓
	CG	BERMAN, E. <i>et al.</i> , "Synergistic cytotoxic effect of azidothymidine and recombinant interferon alpha on normal human bone marrow progenitor cells," <i>Blood</i> , 74(4):1281-1286 (1989)	✓
	CH	BHAT <i>et al.</i> (Oral Session V, Hepatitis C Virus, Flaviviridae, 2003 (Oral Session V, Hepatitis C Virus, Flaviviridae; 16 <sup>th</sup> International Conference on Antiviral Research (April 27, 2003, Savannah, Ga.); p A75).	✓
	CI	BROWNE, M.J., <i>et al.</i> , "2',3'-didehydro-3'-deoxythymidine (d4T) in patients with AIDS or AIDS-Related Complex: A Phase I trial," <i>J. Infect. Dis.</i> , 167(1):21-29 (1993).	✓
	CJ	COLACINO, J. M., "Review article: Mechanisms for the anti-hepatitis B virus activity and mitochondrial toxicity of fialuridine (FIAU)," <i>Antiviral Res.</i> , 29(2-3): 125-39 (1996).	✓
	CK	CUI, L., <i>et al.</i> , "Cellular and molecular events leading to mitochondrial toxicity of 1-(2-deoxy-2-fluoro-1-β-D-arabinofuranosyl)-5-iodouracil in human liver cells," <i>J. Clin. Invest.</i> , 95:555-563 (1995).	✓
	CL	DAVIS, G.L., "Current therapy for chronic Hepatitis C," <i>Gastroenterology</i> 118:S104-S114 (2000).	✓
	CM	De FRANCESCO, R., <i>et al.</i> , "Approaching a new era for hepatitis C virus therapy: inhibitors of the NS3-4A serine protease and the NS5B RNA-dependent RNA polymerase," <i>Antiviral Research</i> , 58: 1-16 (2003).	✓
	CN	De LOMBAERT, S., <i>et al.</i> , "N-Phosphonomethyl dipeptides and their phosphonate prodrugs, a new generation of neutral endopeptidase (NEP, EC 3.4.24.11) inhibitors," <i>J. Med. Chem.</i> , 37:498-511 (1994).	✓

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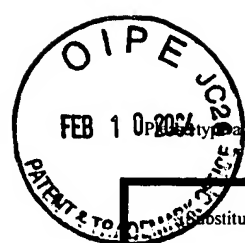
Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	DA	DORNSIFE, R.E., <i>et al.</i> , "In vitro potency of inhibition by antiviral drugs of hematopoietic progenitor colony formation correlates with exposure at hemotoxic levels in Human Immunodeficiency Virus-positive humans," <i>Antimicrob. Agents Chemother.</i> , 40(2):514-519 (1996).	✓
	DB	DYMOCK, B.W., <i>et al.</i> , "Review: Novel approaches to the treatment of hepatitis C virus infection," <i>Antiviral Chemistry &amp; Chemotherapy</i> , 11(2):79-95 (2000).	
	DC	ELDRUP <i>et al.</i> (Oral Session V, Hepatitis C Virus, Flaviviridae; 16 <sup>th</sup> International Conference on Antiviral Research (April 27, 2003, Savannah, Ga.).	✓
	DD	FARKAS, J., <i>et al.</i> , "Nucleic acid components and their analogues. XCIV. Synthesis of 6-amino-9-(1-deoxy-β-D-psicofuranosyl)purine", <i>Collect. Czech. Chem. Commun.</i> 32:2663-2667 (1967).	✓
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	DF	FARQUHAR, D., <i>et al.</i> , "Synthesis and biological evaluation of neutral derivatives of 3-fluoro-2'-deoxyuridine 5'-phosphate," <i>J. Med. Chem.</i> 26: 1153 (1983);	✓
	DG	FARQUHAR, D., <i>et al.</i> , "Synthesis and biological evaluation of 9-[5'-(2-oxo-1,3,2-oxazaphosphorinan-2-yl)-β-D-arabinosyl]adenine and 9-[5'-(2-oxo-1,3,2-dioxazaphosphorinan-2-yl)-β-D-arabinosyl]adenine: Potential neutral precursors of 9-[β-D-arabinofuranosyl]adenine 5'-monophosphate," <i>J. Med. Chem.</i> 28:1358-1381 (1985).	✓
	DH	FERRARI R., <i>et al.</i> , "Characterization of soluble hepatitis C virus RNA-dependent RNA polymerase expressed in <i>Escherichia coli</i> ," <i>Journal of Virology</i> , 73(2), 1649-1654 (1999).	✓
	DI	FISCHL, M.A., <i>et al.</i> , "Zalcitabine compared with zidovudine in patients with advanced HIV-1 infection who received previous zidovudine therapy," <i>Ann. Intern. Med.</i> , 18(10):762-769 (1993).	✓
	DJ	FREED, J.J., <i>et al.</i> , "Evidence for acyloxymethyl esters of pyrimidine 5'-deoxyribonucleotides as extracellular sources of active 5'-deoxyribonucleotides in cultured cells," <i>Biochemical Pharmacology</i> . 38:3193-3198 (1989).	✓
	DK	GUNIC, E., <i>et al.</i> , "Synthesis and cytotoxicity of 4'-C-and 5'-C-substituted Toyocamycins," <i>Bioorg. Med. Chem.</i> , 9:163-170 (2001).	✓
	DL	HARRY-O'KURU, R.E., J.M. Smith, and M.S. Wolfe, "A short, flexible route toward 2'-C-branched ribonucleosides", <i>J. Org. Chem.</i> 62, 1754-1759 (1997). (Scheme 11).	✓
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	EA	HOSTETLER, K.Y., <i>et al.</i> , "Greatly enhanced inhibition of Human Immunodeficiency Virus Type I replication in CEM and HT4-6C cells by 3'-deoxythymidine diphosphate dimyristoylglycerol, a lipid prodrug of 3'-deoxythymidine," <i>Antimicrob. Agents Chemother.</i> , 36:2025-2029 (September 1992).	✓
	EB	HUNSTON, R.N., <i>et al.</i> , "Synthesis and biological properties of some cyclic phosphotriesters derived from 2'-deoxy-5-fluorouridine," <i>J. Med. Chem.</i> 27:440-444 (1984).	✓
	EC	JONES, G. H.; Moffatt, J. G., <i>Methods in Carbohydrate Chemistry</i> ; Whisler, R. L. and Moffatt, J. L. Eds; Academic Press: New York, 1972; 315-322	✓
	ED	JONES, G. H., <i>et al.</i> , "4'-substituted nucleosides. 5. Hydroxymethylation of nucleoside 5'-aldehydes," <i>J. Org. Chem.</i> , 44:1309-1317 (1979).	✓
	EE	KHAMNEI, S., "Neighboring group catalysis in the design of nucleotide prodrugs," <i>J. Med. Chem.</i> , 39:4109-4115 (1996).	✓
	EF	KUCERA, L.S., <i>et al.</i> , "Novel membrane-interactive ether lipid analogs that inhibit infectious HIV-1 production and induce defective virus formation," <i>AIDS Res. Hum. Retro Viruses</i> , 6:491-501 (1990).	✓
	EG	KURTZBERG J., <i>et al.</i> , "Differential toxicity of carbovir and AZT to human bone marrow hematopoietic progenitor cells in vitro," <i>Exp. Hematol.</i> , 18(10):1094-1096 (1990).	✓
	EH	LEONARD, N. J., <i>et al.</i> , "5-Amino-5-deoxyribose derivatives. Synthesis and use in the preparation of "reversed" nucleosides" <i>J. Heterocycl. Chem.</i> , 3:485-489 (December 1966).	✓
	EI	LERZA, R., <i>et al.</i> , "In vitro synergistic inhibition of human bone marrow hemopoietic progenitor growth by a 3'-azido-3'-deoxy-thymidine, 2',3'-dideoxycytidine combination," <i>Exp. Hematol.</i> , 25(3):252-255 (1997).	✓
	EJ	LEWIS W., <i>et al.</i> , "Zidovudine induces molecular, biochemical, and ultrastructural changes in rat skeletal muscle mitochondria," <i>J. Clin. Invest.</i> , 89(4):1354-1360 (1992).	✓
	EK	LEWIS, L. D., <i>et al.</i> , "Ultrastructural changes associated with reduced mitochondrial DNA and impaired mitochondrial function in the presence of 2'3'-dideoxycytidine," <i>Antimicrob. Agents Chemother.</i> , 36(9):2061-2065 (1992).	✓
	EL	LEWIS, W., <i>et al.</i> , "Fialuridine and its metabolites inhibit DNA polymerase $\gamma$ at sites of multiple adjacent analog incorporation, decrease mtDNA abundance, and cause mitochondrial structural defects in cultured hepatoblasts," <i>Proceedings of the National Academy of Sciences, USA</i> , 93(8): 3592-7 (1996).	✓
	EM	LOHMANN V., <i>et al.</i> , "Biochemical and kinetic analyses of NS5B RNA-dependent RNA polymerase of the Hepatitis C virus," <i>Virology</i> , 249, 108-118 (1998).	✓
	EN	LUH, T.-Y., <i>et al.</i> , "A convenient method for the selective esterification of amino-alcohols," <i>Synthetic Communications</i> , 8(5):327-333 (1978).	✓

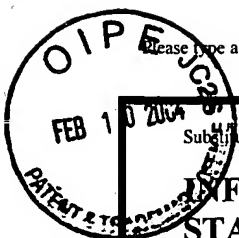
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of

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**Complete if Known**

Application Number	10/609,298
Filing Date	June 27, 2003
First Named Inventor	S mmadosi <i>et al.</i>
Group Art Unit	1623
Examiner Name	Unassigned
Attorney Docket Number	06171.105059 IDX 1017

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**OTHER PRIOR ART – NON PATENT LITERATURE DOCUMENTS**

Examiner Initials *	Cite No. <sup>1</sup>	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published.	T <sup>6</sup>
	FA	McCORMICK, J., <i>et al.</i> , "Structure and total synthesis of HF-7, a neuroactive glyconucleoside disulfate from the funnel-web spider <i>Hololena curta</i> ," <i>J. Am. Chem. Soc.</i> , 121(24), 5661-5664 (1999).	✓
	FB	MCKENZIE, R., <i>et al.</i> , "Hepatic failure and lactic acidosis due to fialuridine (FIAU), an investigational nucleoside analogue for chronic hepatitis B," <i>N. Engl. J. Med.</i> , 333(17):1099-1105 (1995).	✓
	FC	MEDINA, D. J., <i>et al.</i> , "Comparison of mitochondrial morphology, mitochondrial DNA content, and cell viability in cultured cells treated with three anti-Human Immunodeficiency Virus dideoxynucleosides," <i>Antimicrob. Agents Chemother.</i> , 38(8):1824-8 (1994).	✓
	FD	MEIER, C., <i>et al.</i> , "Cyclic saligenyl phosphotriesters of 2',3'-dideoxy-2',3'-didehydrothymidine (d4T) – A new pro-nucleic approach," <i>Bioorganic &amp; Med. Chem. Letters</i> 7(2):99-104 (1997).	✓
	FE	MEYER, R.B., Jr., <i>et al.</i> , "2'-O-Acyl-6-thioinosine cyclic 3',5'-phosphates as prodrugs of thioinosinic acid," <i>J. Med. Chem.</i> 22: 811-815 (1979).	✓
	FF	NEIDLEIN, R., <i>et al.</i> , "Mild preparation of 1-benzyluloxyminoalkylphosphonic dichlorides: Application to the synthesis of cyclic phosphonic diesters and cyclic monoester amides," <i>Heterocycles</i> 35:1185-1203 (1993).	✓
	FG	NUTT, R.F., <i>et al.</i> , "Branched-chain sugar nucleosides. III. 3'-C-methyladenine," <i>J. Org. Chem.</i> , 33:1789-1795 (1968).	✓
	FH	OLSEN, <i>et al.</i> (Oral Session V, Hepatitis C Virus, Flaviviridae; 16 <sup>th</sup> International Conference on Antiviral Research (April 27, 2003, Savannah, Ga.) p A76).	✓
	FH	PAN-ZHOU, X-R., <i>et al.</i> , "Differential effects of antiretroviral nucleoside analogs on mitochondrial function in HepG2 cells," <i>Antimicrob. Agents Chemother.</i> 44:496-503 (2000).	✓
	FJ	PIANTADOSI, C., <i>et al.</i> , "Synthesis and evaluation of novel ether lipid nucleoside conjugates for anti-HIV-1 activity," <i>J. Med. Chem.</i> 34:1408-1414 (1991).	✓
	FK	RICHMAN, D.D., <i>et al.</i> , "The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-Related Complex," <i>N. Engl. J. Med.</i> , 317(4):192-197 (1987).	✓
	FL	SOMMADOSSI J-P., <i>et al.</i> , "Comparison of cytotoxicity of the (-)- and (+)- enantiomer of 2',3'-dideoxy-3'-thiacytidine in normal human bone marrow progenitor cells," <i>Biochemical Pharmacology</i> 44(10):1921-1925 (1992).	✓
	FM	SOMMADOSSI J.-P., <i>et al.</i> , "Toxicity of 3'-azido-3'-deoxythymidine and 9-(1,3-dihydroxy-2-propoxymethyl)guanine for normal human hematopoietic progenitor cells in vitro," <i>Antimicrobial Agents and Chemotherapy</i> , 31:452-454 (1987).	✓
	FN	STARRETT, J.E.Jr., <i>et al.</i> , "Synthesis, oral bioavailability determination, and <i>in vitro</i> evaluation of prodrugs of the antiviral agents 9-(2-(phosphonomethoxy)ethyl]adenine (PMEA)," <i>J. Med. Chem.</i> 37: 1857-1864 (1994).	

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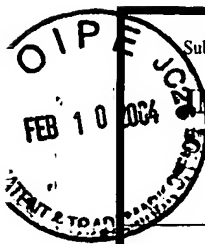
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				Filing Date	June 27, 2003
				First Named Inventor	S mmadossi <i>et al.</i>
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7 of 7				Attorney Docket Number	06171.105059 IDX 1017

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	GA	WEINBERG, R.S., <i>et al.</i> , "Effect of antiviral drugs and hematopoietic growth factors on <i>in vitro</i> erythropoiesis," <i>Mt. Sinai J. Med.</i> 1998;65(1):5-13.	✓
	GB	YARCHOAN, R., <i>et al.</i> "Long-term toxicity / activity profile of 2',3'-dideoxyinosine in AIDS or AIDS-related complex," <i>The Lancet</i> , 336(8714):526-529 (1990).	✓
	GC	YOSHIDA Y, <i>et al.</i> , "Reversal of azidothymidine-induced bone marrow suppression by 2',3'-dideoxythymidine as studied by hemopoietic clonal culture," <i>AIDS Res. Hum. Retroviruses</i> , 6(7):929-932 (1990).	✓
	GD	ZON, G., "Cyclophosphamide Analogues," Chapter 4 in <i>Progress in Medicinal Chemistry</i> , Vol. 19, G.P. Ellis and G.B. West, Eds., pp. 205-246 (1982).	✓

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